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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/839,711	04/20/2001	Darwin J. Prockop	53844-5005	6580

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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 08/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/839,711	PROCKOP ET AL.	
	Examiner	Art Unit	
	Robert M. Kelly	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments and arguments of 6/6/05 are entered.

Claims 1, 5, 9, 13-16, 18-20, 22-24, 26-28 have been amended.

Claims 33-48 are newly added.

Claims 1-48 are pending and considered.

Note: Change in Art Unit and SPE

The Examiner has been reassigned to Art Unit 1633. Therefore, future correspondence should reflect such changes. Also, at the end of the Action is the information regarding the SPE of the Art Unit.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

In light of Applicant's amendments and arguments, the objections to Claims 18-20, 22, 24, and 26-28 under 37 CFR 1.75 as being a substantial duplicate of claims 2-4, 6, 8, and 10-12, respectively, are withdrawn.

Claim Rejections - 35 USC § 112, new matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In light of Applicant's amendments and arguments, the rejections of Claims 1-16, 18-20, 22, 24, and 26-28 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, are withdrawn.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, Applicant's claims now encompass cultured cells that are not modified in any way; however, these cells are inherently modified by the fact that such culturing step is performed to increase their number. Secondly, it is well recognized in the art that cells are modified by cell culture conditions, including influences by growth factors, as evidenced by Bianchi, et al. (2001) Wound Rep. Reg., 9: 460-66. One such modification to actually modifies the cells' engraftment abilities. Therefore, because the term not modified in any way necessarily encompasses these changes, the claims are rejected for containing new matter.

Claims 33-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed

invention. Applicant's new claims 33-48 encompass culturing cells for approximately 5 weeks. Applicant's explicit support in the specification as filed is the listing of various time frames, of which none state approximately 5 weeks, and many time frames do not include 5 weeks (SPECIFICATION, p. 9, paragraphs 1-2). Applicant's implicit support for 5 weeks is the fact it took 5 weeks, under the conditions provided, to perform three passages of MSC (p. 18, last paragraph). However, Applicant's claim is broader, encompassing more, or less, than three passages over 5 weeks. Therefore, considering Applicant's broad explicit support, without particular reference to lead the Artisan to believe Applicant possessed a 5-week culture, and Applicant's implicit support being intrinsically linked to the time it took to obtain 3 passages, the Artisan would not believe Applicant had possession of 5-week cultures with more or less than 3 passages. Hence, Applicant's limitation to 5 week's culturing without also limiting the passages to 3 is properly regarded as new matter.

Response to Argument – new matter

Applicant's argument of 6/6/05 has been fully considered but is not found persuasive.

Applicant argues that the phrase "not modified in any way" is implicitly supported by the specification, in which no transformation of the cells has occurred (Applicant's argument of 6/6/05, p. 11).

Such is not persuasive for the reasons given the rejection above. Applicant has not addressed these specific modifications. Hence, the rejection is held.

Claim Rejections - 35 USC § 102 – Anklesaria

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

In light of Applicant's amendments and arguments, the rejections of Claims 1-2, 4-6, 8-10, 12-16, 18, 20, 22, 24, 26, and 28, under 35 U.S.C. 102(b) as being anticipated by Anklesaria, et al. "Engraftment of a clonal bone marrow stromal cell line *in vivo* stimulates hematopoetic recovery from total body irradiation" (1987) Proc. Natl. Acad. Sci., USA, 84: 7681-85, are withdrawn.

However, if should amend the claims to remove the limitation of "not modified in any way", the rejection may be applied to those claims that contain the limitation.

Claim Rejections - 35 USC § 103 – Anklesaria/Palsson

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-48 remain, or are newly rejected as necessitated by amendment, under 35 U.S.C. 103(a) as being unpatentable over Anklesaria '87 as applied to Claims 1-2, 5-6, and 9-10 above, and further in view of U.S. Patent No. 5,635,386 to Palsson, et al., hereinafter referred to

as "Palsson '386" for reasons of record in the previous Office Actions and/or further for reasons necessitated by the amendments, as evidenced by Shpall, et al. (1997) Annu. Rev. Med., 48: 241-51 and Remes, et al. (1996) Annals Medcine, 28 : 79-81.

Applicant's claims encompass rescuing, enhancing hematopoiesis, enhancing hematopoietic recovery, enhancing hematopoietic stem cell differentiation, increasing survival, and treating mammals, wherein such mammal may have suffered from a lethal dose of total body irradiation or ablated marrow. The methods steps include administration of allogenic stromal cells obtained from a donor, which may be administered immediately or after up to 3 passages in culture, or culturing for approximately 5 weeks, or culturing in vitro without any modification of the cells. Specific dependent claims include treatment of rodents and humans, and the administration of the cells into the patient by infusion.

Ankelsaria '87 teaches engraftment of an allogenic stromal cell line via intraveneous injection (infusion), of irradiated mice (a rodent) (ABSTRACT). Such mice demonstrated increased hematopoesis and significantly enhanced hematopoietic recovery over control mice (ABSTRACT). From this, the Artisan would deduce that allogenic stromal cells are capable of increasing hematopoesis, rescuing animals, enhancing hematopoietic stem cell differentiation, increasing survival, and treating animals, particularly in cases where the bone marrow was ablated. Moreover, it is maintained that the primary purpose of these early experiments with rodents is to extrapolate treatment to humans, as Rodents are generally not thought of in the Art as needing to be rescued from bone marrow ablation or needing increased hematopoiesis. However, Ankelsaria does not specifically teach treating humans, and the specific cells were

transformed with a vector that expresses Neo, for selection of the cells in culture (p. 7682), and therefore, Ankelsaria also does not specifically teach non-modified cells.

On the other hand, Palsson '386 teaches the use of human hematopoeitic stem cells and their cultures that "afford improved methods for bone marrow transplantation." Such cells were already known before Palsson to have been available in the bone marrow (cols. 1-2). Moreover, as in Applicant's specification, Palsson recognizes that the cells are cultured to expand the number of cells for administration, in cases where such is needed, and the cells are administered by infusion (col. 3, paragraph 2). Furthermore, with regard to specific numbers and passages of cells, the requirements are well within the skill in the art, and are simply related to the initially-available number of cells, and the number of cells desired to be transformed (col. 33, paragraph 2). Furthermore, the Artisan would recognize from Palsson, that if expansion was not required, the isolated cells may be administered immediately.

It would have been obvious to practice the invention at the time invention by Applicant. One of skill in the art at the time the invention was made would have been motivated to modify the teachings of Anklesaria '87 with that of Palsson '386, and use human cells in humans to obtain the benefit of rescuing humans having ablated marrow, due to radiation or other reasons, or enhance hematopoeisis, by infusion of the cells, and to further culture the cells as needed to obtain the number of cells required for infusion. Furthermore, the artisan would have had a reasonable expectation of success, as bone marrow transplantation was already known, and the fact that the cultures taught by Palsson '386 were known to afford improved methods for bone marrow transplantation, which necessarily demonstrates that cells themselves may be used in bone marrow transplantation in humans.

While it is maintained that the following references are not required for the rejection, further evidence for such administrations of bone marrow stromal cells are evidenced by Shpall, et al. (1997) Annu. Rev. Med., 48: 241-51, which indicates that hematopoietic progenitor cell support, including the use of bone marrow cells, is well established in humans (ABSTRACT; INTRODUCTION). Moreover, Remes, et al. (1996) Annals Medcine, 28 : 79-81, demonstrates that autologous stem cell support from bone marrow has been known in the art (ABSTRACT; p. 79, col. 2, paragraph 2). Hence, it is obvious in the art that the use of such cells was known, and the use of allogenic cells is obvious given the art cited by the Examiner.

Response to Argument – all art rejections

Applicant's arguments of 6/6/05 have been fully considered but are not found persuasive.

Applicant argues that Ankelsaria teaches a transformed cell line, developing a subclone, and administration of such, and hence Ankelsaria does not anticipate the claims (Applicant's argument of 6/6/05, pp. 12-13, paragraph bridging).

Such argument is noted, but not required, as the rejection on the basis of anticipation is dropped.

Applicant argues that Ankelsaria does not teach the various aspects of the claims as submitted, including culture times, non-transformed cells, and cultures for 3 or less passages. Applicant argues that the invention is an improvement for short-term cultures *per se*, which may be used in lieu of long-term cultures. Therefore, Applicant argues, Ankelsaria is deficient (Applicant's argument of 6/6/05, p. 13, last paragraph).

While the Examiner agrees, as demonstrated by the withdrawal of the rejections under anticipation, that the claims are not taught by Ankelsaria, Applicant's argument is nonetheless

addressed, as part of the obviousness rejection including the Ankelsaria reference. First, Applicant has at no point made clear that their invention is for short-term cultures. In fact, Applicant's specification includes long term culturing of cells to over a year in length (SPECIFICATION, p. 9, paragraph 1). Also, Applicant's claims often claim culturing without limit to time frame. If Applicant does wish to distinguish the invention according to short-term culture versus long-term, Applicant is requested to amend the claims accordingly. Second, with regard to non-transformed cells, Applicant's claims do not require the cells to not be transformed. Also, while Ankelsaria transformed with a vector (although it is unclear whether such cells are rendered immortal) such vector transformation is for purposes of selection; moreover, these cells were shown to be indistinguishable from untransformed cells (p. 7682, col. 1, paragraphs 2-3). Hence, the Artisan would not recognize such structure to limit the disclosure to cells transformed with a selection marker, as these markers have nothing to do with treatment/etc. Therefore, while not explicitly teaching non-transformed cells, certainly makes it obvious to the Artisan. Third, with regard to the number of passages or cultures, the Examiner maintains, as is also shown by Palsson, that the Artisan would know that to expand the number of cells available, you culture for longer times, with more passages, depending on the number of cells you require. Such is trivial in the art, and pure logic, and time-frame simply depends on the number cells you have to expand from, the number of cells you wish to obtain, and the culture conditions. Hence, while not teaching specific passages, the Artisan would walk away from Ankelsaria predicting that other marrow stromal cells could be used in other species, they do not require selection markers/transformations, and depending on the amount of cells you start with,

the amount you want, and the culture conditions, any particular number of passages and time frames may be used.

Applicant argues that Palsson only teaches the cells *per se*. Applicant further argues that Palsson teaches only long-term cultures. Applicant further argues that Palsson does not teach treating total body irradiation. From this, Applicant argues that Palsson does not render the claims obvious, even in view of Ankelsaria (Applicant's argument of 6/6/05, pp. 14-15, paragraph bridging).

Such is not persuasive. First, Palsson may have a long-term culture example, but clearly Palsson indicates that culture times are dependent on the number of cells the Artisan wishes to obtain, given the number they originally have (col. 3, paragraph 2). Further, Applicant has claims that encompass long-term culture, therefore, Applicant does believe the invention encompasses long-term culture. Second, with regard to treating total body irradiation, Palsson teaches that these cells may be used in improved methods for bone marrow transplantation (ABSTRACT), and hence, clearly Palsson encompasses any method of bone marrow ablation, as such is standard in the Art, as evidenced by both Shpall and Remes (ABOVE). Further to this point, Applicant's invention is not treatment of total body irradiation, as Applicant's claims encompass more than just total body irradiation.

Applicant argues again that Ankelsaria is limited to exactly what is taught, i.e., that a mouse may be rescued from total body irradiation by a cell transformed with a retroviral vector including neomycin resistance gene, and that such would not encompass anything else (Applicant's argument of 6/6/05, p. 15, paragraph 2).

Such arguments have been answered above, and they are still not persuasive.

Applicant argues that Palsson does not generate a reasonable expectation of success over that of Ankelsaria, because Palsson teaches long-term culture and no use (Applicant's argument of 6/6/05, p. 15, paragraph 3).

Such is not persuasive, for the reasons given above.

Applicant argues that Ankelsaria and Palsson teach away from Applicant's invention, arguing that the cells are different, referring the above-discussed arguments (Applicant's argument of 6/6/05, p. 15, last paragraph).

Such is not considered persuasive for the reasons given above.

Note to Applicant

Applicant appears to believe that their disclosure of essentially the same thing as Ankelsaria enables their invention at the time of invention, with a breadth of many species and cell types, but that Ankelsaria's invention is not obvious for any more than what is shown in the reference itself, at the time of Applicant's invention. On the hand, the Examiner believes that the art sufficiently demonstrates those aspects claimed by Applicant are enabled by the Ankelsaria reference. Further to this point, if two references disclose the same thing at the same time, they necessarily enable, and therefore provide a reasonable expectation of success for the same subject matter. The Examiner has demonstrated that bone marrow transplants were known in the art, that the stromal cells were the reasons for such transplants, and that other references recognize the utilization of stromal cells in, *inter alia*, humans, even to the point of suggesting a different source for equivalent cells (i.e., peripherial blood). Such suggestion and application of a different source would not be made if the Art did not have the field pretty well characterized. Moreover, with regard to the differences in Ankelsaria, those differences between Ankelsaria and

Applicant's disclosure encompass such structure that would not be detrimental to a reasonable expectation of success (i.e., the transformation yielded cells with equivalent function). Moreover, the whole of the Palsson reference takes for granted that these cells are used in such methods of transplantation. Hence, the only conclusion that can be reasonably made by the Artisan is that Applicant's claimed methods are obvious.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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SPE 1633